

**REMARKS**

Claims 33-36, 39-41, 44, 48-52, 55-56 and 59 are pending. Claim 41 has been amended to depend from claims 33, 50 and 59. Claims 33, 50 and 59 have been amended to clarify that the composition encompassed by the presently claimed methods is formulated without an adjuvant or immunostimulatory agent. Support for this amendment can be found throughout the specification and claims as originally filed, *e.g.*, page 27 (lines 13-16), page 33 (lines 26-29) and original claim 27.

The foregoing claim amendments should in no way be construed as acquiescence to any of the Examiner's rejections and were made solely to expedite prosecution of the application. Applicants reserve the right to pursue claims to the canceled subject matter, or any subject matter which they are entitled to claim, in this or a separate application. *No new matter has been added.*

***Information Disclosure Statement***

Applicants submit herewith an Information Disclosure Statement and corresponding PTO Form SB/08 for the Examiner's consideration.

***Withdrawal of Prior Rejections***

In the present Office Action, the Examiner did not specifically acknowledge withdrawal of the previous rejection of claims 4-43 under 35 U.S.C. § 112, first paragraph, as lacking enablement. However, this rejection under 35 U.S.C. § 112, first paragraph, is not raised in the present Office Action. Therefore, Applicants respectfully assume that this rejection has been withdrawn, and would appreciate confirmation of such by the Examiner.

***Rejection of Claims 33-36, 39-41, 44, 48-52, 55, 56 and 59 Under 35 U.S.C. §103(a)***

The Examiner has maintained the rejection of claims 13-36, 39-41, 44, 48-52, 55, 56 and 59 as being unpatentable over WO 01/85798 in view of US 5,869,057. The Examiner relies on WO 01/85798 as teaching a human monoclonal antibody that binds to the macrophage mannose receptor present on dendritic cells conjugated to a tumor antigen. The Examiner acknowledges that the '798 publication does not teach the use of  $\beta$ hCG as a tumor antigen, but asserts that the '057 patent teaches the use of  $\beta$ hCG as an antigen that "is

detectable on the surface of all tumor cells and could be used in immunization against  $\beta$ hCG and an antimetastasis treatment.” The Examiner concludes that “it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ  $\beta$ hCG as a tumor antigen as taught by the ‘057 patent into a molecular conjugate comprising a human monoclonal antibody that binds to dendritic cells and immunostimulatory cytokine taught by the ‘798 publication.”

In their previous Amendment and Response dated May 21, 2009, Applicants amended the claims to specify a method of inducing or enhancing a cytotoxic T cell response against  $\beta$ hCG comprising contacting antigen presenting cells (APCs) either in vivo or ex vivo with a composition (*i.e.*, containing a monoclonal antibody that binds to human MMR linked to  $\beta$ hCG) that does not include an adjuvant or immunostimulatory agent. Applicants previously argued (and still maintain) that, based on the teachings of the prior art at the filing date of the application, it would not have been obvious that  $\beta$ hCG (*i.e.*, a self protein) could successfully be used as a vaccine to induce or enhance T cell mediated immune responses when targeted via an antibody to the human MMR when formulated without an adjuvant or immunostimulatory agent.

Specifically, as previously discussed, the prior art taught that  $\beta$ hCG-based vaccines must include potent carriers and adjuvants because human  $\beta$ hCG antigen was well known to be “self-tolerant”. For example, as taught by Gupta *et al.*, (*J. Mol. Endocrinol.* 2001 Jun;26(3):281-7; enclosed herewith as Appendix A):

$\beta$ hCG, being a ‘self’ molecule, is ***required*** to be linked to protein carrier molecules to render it immunogenic. Protein carriers have limitations and can be substituted by a combination of helper T-cell peptides (Mandokhot *et al.*, 2000) (emphasis added).

This is supported by Lund and Delves ((1998), Reviews of Reproduction 3:71-76; enclosed herewith as Appendix B), which teaches that:

[t]he glycoprotein hormones are ‘self’ antigens. Although normally expressed only during pregnancy, it appears that hCG is very effective at establishing immunological tolerance. There are hardly any reports of circulating autoantibodies to the hormone being detected in humans, even in patients with a history of recurrent spontaneous abortion (Tulppala *et al.*, 1992). However, it is also clear that this tolerance is not absolute, because when it is ***administered coupled to a potent carrier and in the presence of adjuvant***,

***hCG can break tolerance and elicit an immune response*** (emphasis added)  
(paragraph spanning pages 74-75).

Further evidence that the prior art believed the only relevant form of  $\beta$ hCG vaccine was one wherein  $\beta$ hCG was linked to an immunogen carrier and/or included an adjuvant is provided by Triozzi *et al.* This reference describes conjugates of  $\beta$ hCG-CT coupled to diphtheria toxoid and combined with the adjuvant, muramyl dipeptide and a vehicle, squalene/mannide monooleate (Ann NY Acad Sci (1993) (enclosed as Appendix C).

Importantly, even the patent cited by the Examiner, US 5,869,057, teaches that it is necessary to link a “self” gene product ( $\beta$ hCG epitope) to a microbial (non-self) gene product (*e.g.*, a prokaryotic helper T cell epitope, such as heat-labile enterotoxin B subunit (LTB)), since it is the “natural adjuvant properties of microbial gene products” that are used to illicit an immune response and produce a therapeutically effective vaccine. Therefore, based on the teachings available in the art prior to the filing of the present application, including those set forth in the ‘057 patent, one of ordinary skill would not have been motivated to have used a  $\beta$ hCG vaccine comprising  $\beta$ hCG linked an antibody against the human MMR, without an adjuvant or immunostimulatory agent, as claimed, to induce or enhance a T cell mediated immune response, since it was well known that antibodies are not microbial gene products, and do not have microbial adjuvant properties, such as helper T cell epitopes.

In contrast, Applicants were the first to develop a method of inducing or enhancing a cytotoxic T cell response against  $\beta$ hCG using a  $\beta$ hCG vaccine, which does not require any adjuvants or other agents. Moreover, Applicants were the first to show that by linking  $\beta$ hCG to an anti-MMR-antibody, the conjugates encompassed by the presently claimed methods were capable of presenting the antigen *via* both MHC class I and class II pathways. Specifically,  $\beta$ hCG is targeted to the MMR and processed through both MHC class I and class II pathways. Thus, antigen-specific CTLs (*e.g.*, CD8<sup>+</sup> T cells) are activated, as well as other important effector T cells, including helper T cells (*e.g.*, CD4<sup>+</sup> T cells), resulting in a completely different response (*i.e.*, cytolytic T cells) than that taught in the prior art (*i.e.*, generation of blocking antibodies).

In response, the Examiner asserts in the present Office Action that

Applicant's assertion based on the generic teachings of the requirement of adjuvant for processing and presentation of T cell epitope by APC is misleading. Note that the currently amended claim does not recite presence of foreign T helper epitopes in the conjugate. Further, the claimed method does not preclude administering agent or adjuvant to the composition separately. Even if the claimed composition precludes any means of adjuvant, at any stages of treatment, the claimed invention is still obvious over the combination of the prior art.

Applicants respectfully disagree, since the pending claims explicitly exclude the use of an adjuvant or immunostimulatory agent in the compositions encompassed by the presently claimed methods. However, in a sincere effort to expedite prosecution, the claims have been amended to clarify this aspect. As amended, the claims are drawn to "a composition formulated without an adjuvant or immunostimulatory agent" (*i.e.*, without the use of T helper epitopes from antigens other than the vaccine antigen, *i.e.*, foreign T helper epitopes). Moreover, it was known in the art prior to the filing of the present invention that self-proteins, such as  $\beta$ hCG, in and of themselves do not typically activate a T cell response. Specifically, as described in Dalum *et al.* (*Mol Immunol.* 1997 Nov-Dec; 34(16-17):1113-20); enclosed as Appendix D),

Normally, the presentation of self peptides ***does not lead to stimulation of T cells*** because of tolerance toward MHC associated epitopes derived from the self proteins. A major reason for the non-responsiveness of self reactive B cells could be the lack of direct T-cell help. ***Accordingly, to make self Ags immunogenic, immunostimulatory Th epitopes have been coupled to chemically to the Ags*** (Talwar *et al.*, 1994; Sad *et al.*, 1993; Steinhoff *et al.*, 1994) (emphasis added).

Further, the Examiner states in the present Office Action that "even if the claimed composition precludes any means of adjuvant, at any stages of treatment, the claimed invention is still obvious over the combination of the prior art." The Examiner supports this position by pointing to a passage of the '057 patent which reads:

My invention offers four primary advantages over prior art...  
Second, my invention precludes the need for ***additional adjuvants*** such as muramyl dipeptide in the final vaccine formulation (lines 54-55) (emphasis added).

Based on this, the Examiner concludes that:

Therefore, the prior art recognizes preclusion of additional adjuvant if self and non-self recognition is established using the antigen such as  $\beta$ hCH.

Applicants respectfully disagree. Importantly, the above quotation from the '057 patent cited by the Examiner omits part of the text from column 11, lines 47-64 of the '057 patent. Specifically, the complete text of column 11, lines 53-56 of the '057 patent reads:

Second, **due to the natural action of microbial products**, my invention precludes the need for additional adjuvants such as muramyl dipeptide in the final vaccine formulation. (emphasis added)

Accordingly, the '057 patent does, indeed, teach the use of adjuvants. Specifically, the '057 patent teaches that, at a minimum, “microbial products” (*i.e.*, natural adjuvants) must be included to produce a therapeutically effective vaccine. The '057 patent also notes that adjuvants “must be included in the vaccine formulation in order for processing and presentation of T cell epitopes by specialized antigen presenting cells such as macrophages and dendritic epidermal cells to occur” (col. 11, lines 3-7).

Consistent with this proposition, the vaccine described in the '057 patent includes both a self antigen (*i.e.*,  $\beta$ hCG) and a non-self microbial product (*i.e.*, *E. coli*. heat-labile enterotoxin subunit B (LTB)), which has “natural” adjuvant properties. Thus, the '057 patent in fact teaches away from the presently claimed invention by explicitly acknowledging that at least a microbial product (*i.e.*, “natural” adjuvant) is required in order to produce an effective vaccine and induce a cytotoxic T cell response against  $\beta$ hCG. In contrast, the composition (*i.e.*, an anti-MMR antibody linked to  $\beta$ hCG) encompassed by the presently claimed methods is formulated without any adjuvants or immunostimulatory agents, (including microbial products or other foreign T helper epitopes).

For at least the foregoing reasons, the presently claimed methods are patentable in view of the cited references, as well as knowledge available in the art prior to the filing of the present application. Moreover, Applicants respectfully submit that the findings which form the basis of the present invention were completely unexpected and would not have been obvious to one of ordinary skill in the art. Accordingly, Applicants respectfully request that this section 103 rejection be reconsidered and withdrawn.

**CONCLUSION**

If the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. CDJ-301RCE3.

Dated: February 11, 2010

Respectfully submitted,

Electronic Signature: /Jill Gorny Sloper/  
Jill Gorny Sloper  
Registration No.: 60,760  
LAHIVE & COCKFIELD, LLP  
One Post Office Square  
Boston, Massachusetts 02109  
(617) 227-7400  
(617) 742-4214 (Fax)  
Attorney/Agent For Applicant